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Modeling malaria and typhoid fever co-infection dynamics

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ABSTRACT

Malaria and typhoid are among the most endemic diseases, and thus, of major public health concerns in tropical developing countries. In addition to true co-infection of malaria and typhoid, false diagnoses due to similar signs and symptoms and false positive results in testing methods, leading to improper controls, are the major challenges on managing these diseases. In this study, we develop novel mathematical models describing the co-infection dynamics of malaria and typhoid. Through mathematical analyses of our models, we identify distinct features of typhoid and malaria infection dynamics as well as relationships associated to their co-infection. The global dynamics of typhoid can be determined by a single threshold (the typhoid basic reproduction number, $\mathcal{R}_0^T$) while two thresholds (the malaria basic reproduction number, $\mathcal{R}_0^M$, and the extinction index, $\mathcal{R}_0^{MM}$) are needed to determine the global dynamics of malaria. We demonstrate that by using efficient simultaneous prevention programs, the co-infection basic reproduction number, $\mathcal{R}_0$, can be brought down to below one, thereby eradicating the diseases. Using our model, we present illustrative numerical results with a case study in the Eastern Province of Kenya to quantify the possible false diagnosis resulting from this co-infection. In Kenya, despite having higher prevalence of typhoid, malaria is more problematic in terms of new infections and disease deaths. We find that false diagnosis—with higher possible cases for typhoid than malaria—cause significant devastating impacts on Kenyan societies. Our results demonstrate that both diseases need to be simultaneously managed for successful control of co-epidemics.

1. Introduction

Over the past three to four decades, malaria has been a major cause of death and illness among children and adults in many developing countries. Approximately 300–500 million cases occur worldwide each year, with more than a million annual deaths [5,37,52]. About 80% of these cases and 90% of these deaths occur in Sub-Saharan Africa [16,19,46]. While malaria is already causing devastating impacts on the tropical developing countries, typhoid fever is quite common in the malaria affected areas, thereby drastically exacerbating the public health burden. Worldwide, over 21 million cases and more than a half million typhoid related deaths occur each year, with most of them taking place in Africa [2,11,23,32]. While people in tropical communities are living at risk of contracting both diseases (either concurrently or an acute infection superimposed on a chronic one [10]), misleading diagnosis due to similar symptoms of these diseases and incompetent testing methodologies is one of the biggest challenges for their control [16,46]. Thus studies of malaria and typhoid are becoming increasingly important.

Malaria is acquired and transmitted to humans through bites by infected anopheles mosquitoes, whereas typhoid is caused by the gram-negative-bacterium of the genus salmonella [16,53], known as *Salmonella Typhi*, through ingestion of foods and drinks contaminated by infected waste. Despite differences in causes and routes of transmission, malaria and typhoid have interesting relationships causing public health encumber, which can be discussed in two broad categories: real co-infection and false diagnosis.

It is known that anemia occurs in malaria infected individuals resulting in excessive deposition of iron in the liver, which supports the growth of salmonella bacteria that causes typhoid fever [8,37]. Moreover, malaria infected individuals suffer from deficiency of complements such as C3, C4, and C19 [37], and the complement deficiency causes an enhanced susceptibility to salmonella infection [9,51]. Therefore, infection due to malaria leads to an increased susceptibility of typhoid. Complements are consumed during malaria infection, impairing host defense mechanisms thereby slowing down any anticipated disease recovery [35]. Furthermore, co-infected individuals have a higher chance of dying because of infections due to both diseases.

While real malaria–typhoid co-infections mentioned above pose significant problems, false diagnosis often resulting in mismanagement of these diseases remains one of the biggest public health

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burdens. Malaria and typhoid exhibit similar signs and symptoms such as fever, headache, vomiting, diarrhoea, and abdominal and muscle pain among others [21,34]. This, in many cases, entices physicians to relate these signs and symptoms with a wrong disease, leading to false diagnosis. Moreover, many existing testing methods, including the most commonly used Widal test [2], frequently generate false positive results. For example, in one study [16] the Widal test showed about 57% of typhoid positive cases whereas truly only 15% were found to have typhoid when more reliable bacteria-culture tests were performed. Despite being more accurate, the bacteria-culture test is not commonly used in practice because of higher costs and longer processing time [37]. This high likelihood of typhoid false positive results in malaria patients from the Widal test is due to a cross reaction between malaria parasites and typhoid antigens [37]. Such false diagnoses may lead to mismanagement of these diseases, posing a vast challenge toward controlling them. For instance, giving antibiotics to seemingly typhoid patients, when they actually have malaria, not only leads to waste of drugs but also may cause emergence of drug resistance in the event of true future typhoid infection. It is thus critical to understand the impact of real co-infection as well as false diagnosis on the disease dynamics.

Mathematical modeling of malaria dynamics is quite advanced [4,6,13,14,26,28]. However, modeling of typhoid fever is very limited [1,31]. While these existing models have provided significant insights into the understanding of individual disease dynamics, they need to be considered simultaneously for devising proper strategies to mitigate both disease burdens. Recently, a study [30] has provided a malaria–typhoid co-infection model, which only considers direct transmission of typhoid (person-to-person) and assumes no recovery of co-infected individuals from single diseases. In this study, we first develop an improved realistic typhoid model. Then based on our new typhoid model and existing standard malaria model, we further develop a co-infection model that captures the dynamics of malaria and typhoid together. Using our model, we develop a formula for the co-infection basic reproduction number, and compare it with the basic reproduction number of individual diseases. We analyze the models for stability of equilibria and persistence of diseases. Furthermore, using parameters relevant to the Eastern Province of Kenya, we study real co-infection dynamics and estimate the possible false diagnosis which poses a big challenge to controlling these diseases.

2. Model formulation

We first develop a more realistic model for typhoid. The model subdivides the human population of interest into four compartments: susceptible humans (S), infected humans (I), carrier humans (C), and recovered humans (R). Previous models of typhoid dynamics [1,30,31], including the one describing malaria–typhoid co-infection [30], assume direct transmission of typhoid from infected individuals to susceptible individuals. However, typhoid is largely contracted from environmental bacteria through contaminated water and/or food and drinks [7,46], and transmission of typhoid through direct person-to-person contact, if any, is negligible [20,50]. To incorporate this real biological phenomena, we consider an additional compartment, B, which represents bacteria in the environment. We assume that susceptible individuals get infected with typhoid at a rate proportional to the susceptible population, S, and the environmental bacteria concentration, B, at a constant rate β. The infected individuals either progress to carrier class, C, at rate α_t or recover at rate η. Individuals in the carrier class can also recover from typhoid, but with a significantly slow rate, γ. Infected individuals in both infectious state and carrier state excrete bacteria into the environment. However, the rate of excretion by the infectious group, p_i, is significantly higher than that by the carrier group, p_c. Note that despite low excretion of bacteria by the carrier group, because of its extremely long duration without showing any sickness the carrier group plays an important role on co-infection dynamics of malaria and typhoid. Growth curves of organisms are often described well with the logistic models [17,22,33,36,47,49], so we assume that the bacteria in the environment grows according to a logistic growth rate and becomes non-infectious at a rate μ_b. r and κ represent per capita growth rate and carrying capacity, respectively, and λ denotes the typhoid induced mortality in humans. The constant recruitment rate into the susceptible human is represented by Λ_h, while the natural death rate of human is represented by μ_h. The developed model can be expressed as the following differential equations.

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda_h - (\beta B + \mu_h)S,\\
\frac{dI}{dt} &= \beta BS - (\mu_h + \lambda + \alpha_t + \eta)I,\\
\frac{dC}{dt} &= \alpha_t I - (\mu_h + \lambda + \gamma)C,\\
\frac{dR}{dt} &= \eta I + \gamma C - \mu_h R,\\
\frac{dB}{dt} &= rB\left(1 - \frac{B}{\kappa}\right) + p_i I + p_c C - \mu_b B.
\end{aligned} \tag{2.1}$$

Similar to the previous studies [4,6,13,14,26,28], we consider a malaria model consisting of four human compartments (susceptible, S, exposed, E, infected, I, and recovered, R) and three mosquito compartments (susceptible, S_m, exposed, E_m, and infected, I_m). In this model, new infected humans are generated by mosquito-bites at an effective biting rate, $\alpha_{mh} b_m$, where α_{mh} denotes the infection probability, per bite, from an infectious mosquito to a susceptible human and b_m denotes the total number of mosquito bites per mosquito per day. Similarly, new infected mosquitoes are generated at an effective biting rate, $\alpha_{hm} b_m$, when susceptible mosquitoes bite infected humans. Here, α_{hm} denotes the probability of successful transmission of malaria from the human to the mosquito, per mosquito bite. The rates at which humans and mosquitoes progress from the exposed class to the infectious class are denoted by δ_h and γ_m, respectively. We define α_h as the rate at which individuals infected with malaria recover from the disease and ω as the malaria induced mortality in humans. The constant recruitment rate into the mosquito populations is represented by Λ_m, while the death rate of mosquito populations is represented by μ_m, respectively. The model we study is as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda_h - \frac{\alpha_{mh} b_m I_m}{N_h} S - \mu_h S,\\
\frac{dE}{dt} &= \frac{\alpha_{mh} b_m I_m}{N_h} S - (\mu_h + \delta_h)E,\\
\frac{dI}{dt} &= \delta_h E - (\mu_h + \alpha_h + \omega)I,\\
\frac{dR}{dt} &= \alpha_h I - \mu_h R,\\
\frac{dS_m}{dt} &= \Lambda_m - \mu_m S_m - \frac{\alpha_{hm} b_m I}{N_h} S_m,\\
\frac{dE_m}{dt} &= \frac{\alpha_{hm} b_m I}{N_h} S_m - (\mu_m + \gamma_m)E_m,\\
\frac{dI_m}{dt} &= \gamma_m E_m - \mu_m I_m.
\end{aligned} \tag{2.2}$$

Based on our novel typhoid model (2.1) and existing malaria model (2.2), we now develop a co-infection model using the four states of typhoid and the four states of malaria. A schematic diagram of the model is shown in Fig. 1. The total human population is therefore subdivided into sixteen mutually exclusive, collectively exhaustive compartments: typhoid-susceptible and malaria-susceptible (X_{SS}); typhoid-susceptible and malaria-exposed (X_{SE}); typhoid-susceptible and malaria-infected (X_{SI});